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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIU, SAMUEL W	
ART UNIT	PAPER NUMBER
1653	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,679	LENTING ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2001 and 03 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *6-14,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 15-17* is/are rejected.

7)☒ Claim(s) *2,16 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' petition for revival of this application filed 13 July 2001 (Paper. No.3) is acknowledged and entered. And, applicants' petition for extension of time of three months filed 3 March 2003 (Paper No. 10) have been entered.

Claims 1-19 are pending.

Election/Restrictions

Applicants' election (filed 3 March 2003, Paper No. 11) of Group I, claims 1-5 and 15-17 without traverse is acknowledged. Claims 6-14 and 18-19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention for the reasons stated above and in the restriction requirement. Therefore, claims 1-5 and 15-17 are under examination to the extent that they are drawn to the elected invention.

Specification/Claim Objections

The disclosure is objected to because of the following informalities:

In page 16, line 3 of [0063], "CMV", "RSV", "HSV' and "hGH" should be spelled out in full for the first instance of use. See also page 16, line 3, "BHK" and "Sk-Hep 1"; and page 16, line 3 of [0063], "EBV".

In page 15, lines 19, line 4 of [0070], "dissociation speed constant" should be changed to "dissociation rate constant", and "affinity constant" in line 6 of the same paragraph is advised to be changed to "equilibrium constant" because not always K_d stands for an affinity constant in kinetics whereas term equilibrium constant is widely accepted.

In claim 2, the recitation "between amino acids 2033 and 2172" should be changed to between amino acids 2033 (Arg) and 2172 (Ile) for a consistency of the current disclosure.

In claims 16 and 17, "RAP" and "LRP" should be spelled out in full as being the first recited in the claims.

In claim 17, "affinity to a Factor-LRP binding site" should be changed to "affinity to a low density lipoprotein receptor binding site of Factor VIII".

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 1-5 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-5, as written, do not distinguish the claimed polypeptides from naturally existing products. The claims do not particularly point out any differences indicating the hand of man. In the absence of the hand of man, the claimed products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, *e.g.*, by insertion of "isolated" or "recombinantly produced " as disclosed on pages 31-33 wherein indicate the disclosed polypeptides are obtained from protein engineering. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-5 and 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the binding affinity without reciting for what subject the binding affinity is; thus, such the recitation renders the claim indefinite. Also, claim 1 recites "modification to said polypeptide ..."; the recitation is unclear as to (i) to what types of modification the recitation refer, e.g., mutational modification (substitution, insertion, and deletion) or *post-translational modification,* e.g., glycosylation, or *chemical modification*, e.g., amidation; (ii) whether or not the modification occurs in each cited region, or in a particular region, or between the regions (*e.g.*, a covalent cross-linking between the region of residues 1942 - 1947 and the region of residues 1959-1974). The dependent claims are also rejected; and (iii) whether or not the resultant modified-polypeptide retains the same or comparable binding affinity for low density lipoprotein receptor, or has increased or decreased binding affinity thereof. The dependent claims are also rejected.

Claims 2-5 is indefinite in recitation "<u>further</u> including ... modification to said polypeptide...". It is not apparent reading whether or not based upon the modification set forth inn claim 1 such the recitation further introduces additional modification into the modified-polypeptide.

Claim 16 is unclear as to "RAP"; does "RAP" refer to tripeptide Arg-Ala-Pro or a particular molecule? Claim 16 recites "soluble fragments"; the recitation is vague regarding whether or not the fragments encompass any proteolytic fragments of low density lipoprotein (LDL) receptor (A membrane protein receptor), or soluble domain (i.e., non-membrane bound domain) of the LDL receptor, or any peptide or polypeptide which length is larger than dipeptide derived from LDL receptor. Additionally, claim 16 is indefinite for depending from claim 13 that is non-elected. Further, claim 16 is unclear as to whether or not "lipoprotein receptor protein" refers to the low density lipoprotein receptor recited in claim 15, or any type of lipoprotein receptor, e.g., megalin (see Willnow, T. E. et al. (1999) Nature, Cell biology, 1, E157-E162).

Claim 17 is indefinite for depending from the non-elected claim 14.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Eaton, D. L. (*Biochemistry* (1986) 25, 8343-8347).

Eaton et al. teach a Factor VIII mutant molecule comprising residues 797-1562 lacking the light chain (form amino acid residue 1649 to residue 2332, i.e., A3-C1-C2 domains); the mutant molecule has Factor VII:C activity (see abstract and Figures 1 and 5), which meets the

limitation set forth in the claim because claim 1 recites "containing at least one modification ..."; such the recitation encompasses deletion medication of the Factor VIII domains.

Because structural feature is inherent property of a biomolecule, the above-stated mutational change (deletion) would have influence on the mutant binding to low density lipoprotein receptor protein (LRP). It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Therefore, Eaton et al. reference anticipates claim 1 of the instant application.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Lollar, J. S. (US Pat. No. 5364771) as is evidenced by the known fact disclosed in the specification on page 3, line 5.

Lollar et al. teach a hybrid Factor VIII molecule that a fusion between porcine light chain and human heavy chain wherein the light chain, i.e., amino acids 1649-2332, of human Factor VIII is modified via substitution of porcine light chain for the corresponding human light chain (see Table II and abstract).

Because structural feature is inherent property of a biomolecule, the above-stated mutational change (deletion) would have influence on the mutant binding to low density lipoprotein receptor protein (LRP). It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties

applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The Lollar et al. teaching thus meets the limitation of claim 1 of the instant application. Note that the light chain corresponding to amino acids 1649-2332 is manifested in this specification on page 3, line 5, and note that porcine Factor VIII and human Factor VIII have identical domain organization (see column 6, lines 1-9) in spite of their different potency in coagulant activity (see table I, column 10). Therefore, Lollar et al. patent anticipates claim 1 of the current application.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Lenting P. J. et al. (*J Biol Chem.* (1999) 274, 23734-23739) as is evidenced by the known fact disclosed in Figure 1 of Liu, M. L. reference (Blood (2000) 96, 979-987).

Lenting et al. teach a functional recombinant C2 domain of Factor VIII, which is capable of binding to LRP (see Figure 5). Note that the C2 domain refers to amino acid residue 2173 to residue 2232, which is indicated by Figure 1 of Liu et al. reference, and that claim 1 is directed to modifications involved in residues 1743-2173. The lenting's recombinant protein of C2 domain is thus a truncation variant of the intact Factor VIII, which has structural modification, i.e., truncation, in region of residues 1743-2173. The lenting's teaching meets limitation of the application claim 1.

Because structural feature is inherent property of a biomolecule, the above-stated mutational change (deletion) would have influence on the mutant binding to low density lipoprotein receptor protein (LRP). It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are

inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Thus, Lenting et al. anticipate claim 1 of the current application.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 15 are rejected under 35 U.S.C. 103(a) as being obvious over Lollar J. S. et al. (US Pat. No. 536771) taken with Lenting P. J. et al. (*J Biol Chem.* (1999) 274, 23734-23739) and Schwarz, H. P. et al. (Blood (2000, March) 95, 1703-1708).

Lollar et al. teach a hybrid Factor VIII molecule that is a fusion between porcine light chain and human heavy chain wherein the light chain, i.e., amino acids 1649-2332, of human Factor VIII is modified via substitution of human light chain by the corresponding porcine light

chain (see Table II and abstract). Note that the light chain corresponds to amino acids 1649-2332 is indicated by this specification on page 3, line 5, and that porcine Factor VIII and human Factor VIII have identical domain organization (i.e., A1-A2-B-A3-C1-C2) structural characteristics (see the patent column6, lines 1-9) despite their differing in potency of coagulant activity (see table I, column 10). Thus, the Lollar et al. teaching meets the limitation of claim 1 of the instant application because of the same reasons stated *supra* (see the claim rejection under 35 USC 102 (b) over Eaton et al.).

Also, Lollar et al. teach a pharmaceutical composition comprising the hybrid Factor VIII molecule (see column 6).

Lollar et al. do not explicitly teach the composition comprises a LRP antagonist.

Lenting et al., however, teach human Factor VIII light chain has at least same binding affinity for LRP as does human holo-Factor VIII protein (see Table I). Also, Lenting et al. demonstrate that the affinity of the Factor VIII polypeptide for antagonist "RAP" is approximately 0.5 nM (see panel A of Figure 2) using surface plasma resonance technology which measures real time protein-protein interaction. The Lenting et al. teaching is applied to claim 15 of the current application.

It would have been obvious to one of ordinary skill in the art at the time the invention was made would have combined the teachings of the above references because (i) Lenting et al teach that the antagonist RAP suppresses cellular degradation of Factor VIII (see Figure 3), i.e., the RAP antagonist increases biological half-life of the Factor VIII protein, and (ii) Lollar et al. teach a pharmaceutical composition comprising the hybrid Factor VIII polypeptide which is

much more potent than parent human Factor VIII in view of their Factor VIII:C activity (see Table II, and the bridging columns 12-13).

Further, when combined, there would have been the following advantages: (1) the recombinantly purified Factor VIII can overcome the drawback of purified non-recombinantly purified human Factor VIII due to problems of impurities and viral contamination (see column 1, lines 51-65) as taught by Lollar et al.; (2) an appreciable benefit of using RAP (receptor associated protein), a LRP antagonist, for treating disease state (e.g., von willebrand disease) due to the effect of RAP on inducing sustained rise in Factor VIII level comparable to that induced by von Willebrand factor (vWF) as taught by Schwarz et al. (see abstract and page 1703), and (3) the recombinantly purified Factor VIII is suitable for formulating into a pharmaceutical composition as taught by Lollar et al. (see column 6, lines 24-58) and for a formulation combined with a stabilization compound, *e.g.*, vWF (see column 6, lines 59-65) and RAP (taught by Schwarz et al., see the above statement).

Given the above motivation, one of ordinary skill in the art would have combined the teachings of the above references to arrive at the disclosed invention with respect to a composition comprising a molecule of Factor VIII that interacts with LRP and an antagonist of LRP (i.e., RAP) that functions to reduce cellular clearance, i.e., enhance biological stability, of the Factor VIII. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.

June 10, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER